LA-UR 77-2625

TITLE: The IgM-IgG Switch Looked at From a Control Theoretic Viewpoint

CONF-771012-1

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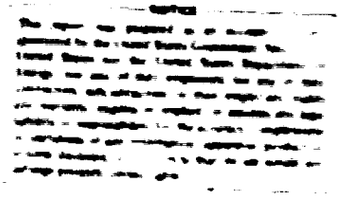
SUBMITTED TO: Proceedings of IFIP Optimization Conference in Nurnburg, Germany held September 1977.



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THE IgM-IgG SWITCH LOOKED AT FROM A CONTROL THEORETIC VIEWPOINT

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The vertebrate immune system is a collection of molecules and cells designed to defend an animal from disease causing agents. When an *antigen* (a foreign molecule either in solution or on a cell) is introduced into an animal it stimulates a class of white blood cells, *B lymphocytes*, to proliferate and to produce protein molecules known as *antibodies*. Antibodies specifically bind to the antigen and lead to its elimination from the animal. One curious feature of the antibody response to an animal's first encounter with antigen (the primary immune response) is that under many circumstances two distinct types of antibody molecule are made, immunoglobulin M (IgM) and immunoglobulin G (IgG). If the amounts of IgM and IgG in the blood serum of an animal are measured as a function of time after injection of antigen, one finds that IgM appears in the blood serum first and IgG appears after some delay. Other analyses which I shall not discuss here have shown that single B lymphocytes first make IgM and then switch to the production of IgG. One further noteworthy feature of this switch is that both the IgM and IgG made by a single cell have the same specificity for antigen (see Figure 1).

In this paper I shall address the question: why should a cell make two different types of antibody with the same specificity for antigen? Further, why should a cell first make one type of antibody (IgM) and then switch to the production of another type (IgG) later in the immune response? Since biological systems are the result of millions of years of evolution by natural selection one might hypothesize that the IgM-IgG switch provides some advantage to an animal. In order to examine this possibility I, in collaboration with Byron Goldstein of Los Alamos Scientific Laboratory and Sol Recklin of the University of California at Berkeley, have devised a model of the interaction of the immune system with a growing antigen (e.g., pathogen) and have attempted to optimize the performance of the immune system with respect to its antibody production. Although there are many pitfalls in using optimization

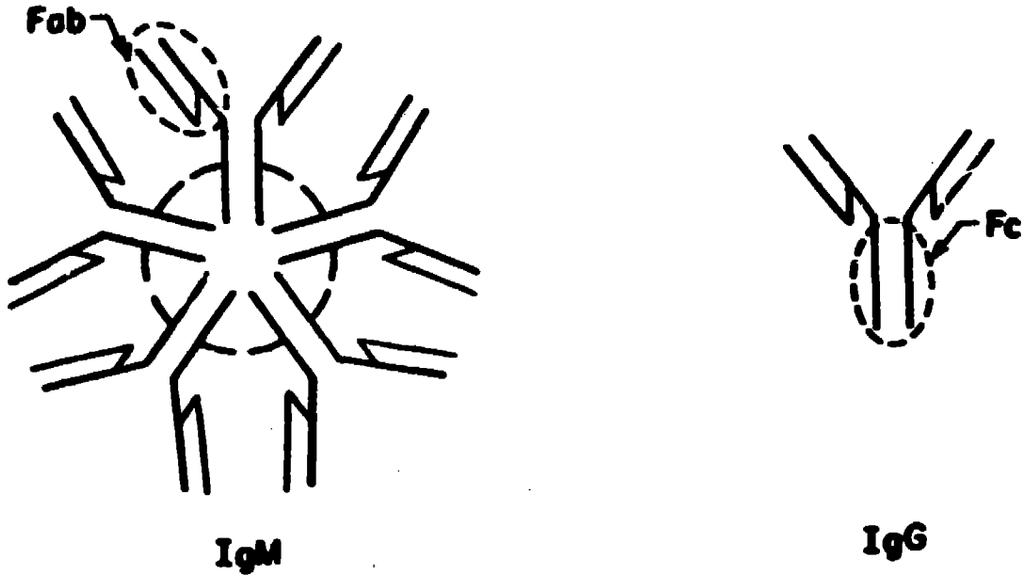

Figure 1. The structure of IgM and IgG. IgM contains five subunits joined by disulfide bridges (circular dotted line, and a J chain (not shown). Each subunit is similar to a single IgG. When a cell switches from IgM to IgG production, both immunoglobulins are believed to contain identical antigen binding fragments (Fab), but different complement binding fragments (Fc).

and Oster, 1976; Oster and Wilson, 1978), the evolutionary stability of the immune system and the magnitude of the selective forces acting on it give one some confidence in the predictions of optimization procedures.

There are many host defenses that act against disease causing organisms (cf Mims, 1976). Here I shall only discuss one defense mechanism, complement dependent lysis which I have singled out because it relies on both IgM and IgG. Besides directly interacting with antigen to form large antibody-antigen aggregates, antibody also acts as a tag, marking cells as foreign. Once a cell is so marked it may be engulfed by a large migratory phagocytic cell such as a neutrophil or macrophage or it may be attacked by a series of eleven serum glycoproteins known as complement. The complement components literally drill a hole in the cell membrane leading to the death of the cell by osmotic forces (cf Mayer, 1973). Not all cells are susceptible to complement dependent lysis (some cells may be able to repair the damage to their membranes), but gram-negative bacteria and virus infected cells are among those which succumb to complement (Osler, 1976; Porter, 1971).

The cascade of binding reactions which eventually can lead to cell lysis is initiated by the first complement component, C1, binding to one IgM

or a pair (or higher multiples) of IgG molecules in close proximity on the cell membrane (Borsos and Rapp, 1965a,b). Studies by Humphrey and Dourmashkin (1965) and Humphrey (1967) showed that for a red blood cell about 800 IgG molecules would be required to attach at random for there to be an even chance that two such molecules would be at adjacent sites. Thus, at least for red cells, it would at first sight seem best if the immune system secreted only IgM. For a pathogen smaller than a red blood cell, c, the critical number of IgG molecules required to bind in order to initiate the complement reaction would be smaller than 800, and should scale roughly as the ratio of the surface area of the pathogen to that of the red blood cell (assuming equal densities of antigenic determinants).

Although IgM and IgG have the same specificity for antigen they need not bind to a cell with equal efficiencies. As shown in Figure 1, IgG has two binding sites, while IgM being a pentamer has ten binding sites. Studies of the dynamics of red cell lysis by IgM and IgG in the hemolytic plaque assay have indicated that IgM rapidly binds and dissociates from the cell surface with an equilibrium constant indicative of single site interaction (Goldstein and Perelson, 1976; Perelson, 1975a,b), whereas IgG is known to bind bivalently to surfaces (Fernick and Karush, 1972). If one assumes that IgG binds bivalently and IgM binds monovalently then the equilibrium constant for IgG binding may be as much as 10^4 times as great as that of IgM, implying that a cell in a solution containing equal concentrations of IgM and IgG would be much more likely to have 800 IgG molecules than 1 IgM molecule on its surface. When there exists such large differences in the binding constants of IgM and IgG it would seem advantageous if the immune system secreted only IgG. However, during the initial stages of an immune response there may not be enough antibody to put 800 molecules of IgG on each pathogen's surface and, in fact, with large infections this may take some time. During this initial period only IgM can lead to cell lysis and thus first producing IgM and the producing IgG may in fact be an optimal strategy.

Model

Consider two populations of lymphocytes, one of which, L_M, secretes only IgM, and the other of which, L_G, secretes only IgG. At any time t, I shall assume that a fraction $\alpha(t)$ of the L_M cells are proliferating with per capita rate b and the remaining fraction of L_M cells are differentiating with per capita rate d into L_G cells. In order not to bias the

model. I shall also assume that a fraction, v(t), of L_G cells are proliferating at per capita rate b and the remaining fraction, 1 - v(t), are differentiating with per capita rate d into L_M cells (Figure 2).

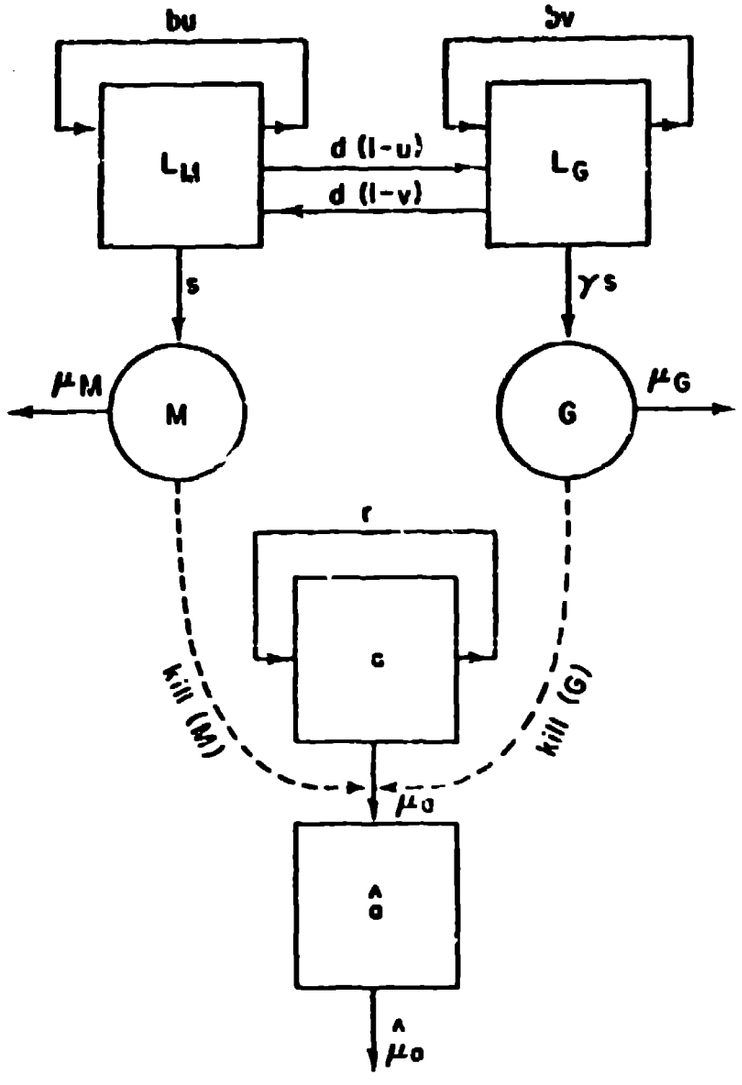

Figure 2. Block diagram of complement dependent killing. The dotted lines indicate portions of the model involving the binding of IgM and IgG to the antigen and the subsequent cell killing. Also the loss of IgM and IgG by the elimination of dead antigen is not shown.

I further assume L_M cells secrete IgM at rate s and L_G cells secrete IgG at a rate γs, where $\gamma \geq 1$ is introduced to account for the difference in size and complexity of the two antibodies. (For example, since IgM is a pentamer it may be possible to secrete 5 times as many IgG molecules as IgM molecules.) The antigen, a, I assume can grow at a per capita net rate r in the absence of antibody and complement and is

killed at a per capita rate μ_a multiplied by p_{kill}, the probability of lysis by complement. Once complement has acted to kill a cellular antigen, the dead cell, $\hat{a}$, is assumed to remain in the system until it is removed, say by phagocytosis, at per capita rate $\hat{\mu}_a$.

To complete the model I need to specify how antibody binds to cells and the probability of a cell being killed by complement dependent lysis. I shall assume that each antigen (cell) has a total of $\tilde{\rho}_0$ sites at which antibody can bind, and the concentrations of sites bound by IgM and IgG on live and dead antigens are ρ_M, ρ_G, $\hat{\rho}_M$ and $\hat{\rho}_G$, respectively. As the antigen grows the total number of available sites in the system, $a\tilde{\rho}_0$, increases, but as dead cells are removed so are sites and antibodies bound to the dead cells. IgM is assumed to bind with only one of its ten sites while IgG is assumed to bind bivalently. The forward and reverse rate constants for the binding reactions of IgM and IgG are k_M, k'_M, k_G and k'_G, respectively. With this set of assumptions one obtains the following state equations:

$$\dot{L}_M = bu(t)L_M - d[1 - u(t)]L_M + d[1 - v(t)]L_G \tag{1}$$

$$\dot{L}_G = bv(t)L_G - d[1 - v(t)]L_G + d[1 - u(t)]L_M \tag{2}$$

$$\dot{M} = sL_M - \mu_M M - \hat{\mu}_a \hat{\rho}_M \tag{3}$$

$$\dot{G} = \gamma s L_G - \mu_G G - \hat{\mu}_a \hat{\rho}_G/2 \tag{4}$$

$$\dot{a} = ra - \mu_a a\, p_{kill} \tag{5}$$

$$\dot{\hat{a}} = \mu_a a\, p_{kill} - \hat{\mu}_a \hat{a} \tag{6}$$

$$\dot{\rho}_M = 10k_M(M - \rho_M - \hat{\rho}_M)(\tilde{\rho}_0 a - \rho_M - \rho_G) - k'_M \rho_M - \mu_a \rho_M\, p_{kill} \tag{7}$$

$$\dot{\hat{\rho}}_M = 10k_M(M - \rho_M - \hat{\rho}_M)(\tilde{\rho}_0 \hat{a} - \hat{\rho}_M - \hat{\rho}_G) - k'_M \hat{\rho}_M + \mu_a \rho_M\, p_{kill} - \hat{\mu}_a \hat{\rho}_M \tag{8}$$

$$\dot{\rho}_G = k_G(2G - \rho_G - \hat{\rho}_G)(\tilde{\rho}_0 a - \rho_M - \rho_G) - k'_G \rho_G - \mu_a \rho_G\, p_{kill} \tag{9}$$

$$\dot{\hat{\rho}}_G = k_G(2G - \rho_G - \hat{\rho}_G)(\tilde{\rho}_0 \hat{a} - \hat{\rho}_M - \hat{\rho}_G) - k'_G \hat{\rho}_G + \mu_a \rho_G\, p_{kill} - \hat{\mu}_a \hat{\rho}_G \tag{10}$$

and probability of being killed by complement, p_{kill}, is given by

$$p_{kill} = p_M + p_G - p_M p_G \tag{11}$$

Here $p_M = p_M(\rho_M, a)$ and $p_G = p_G(\rho_G, a)$ are the probabilities of an antigen being killed with IgM and IgG, respectively. Since $\hat{\rho}_M \triangleq \hat{\rho}_M/a$ is mean number of IgM molecules bound per antigen, p_M, i.e., the probability of having at least one IgM bound to each antigen, is given by

$$p_M(\rho_M, a) = \sum_{i=1}^{\tilde{\rho}_0} \binom{\tilde{\rho}_0}{i} \left(\frac{\tilde{\rho}_M}{\tilde{\rho}_0}\right)^i \left(1 - \frac{\tilde{\rho}_M}{\tilde{\rho}_0}\right)^{\tilde{\rho}_0 - i} \approx 1 - \exp(-\tilde{\rho}_M) \tag{12}$$

while the probability of having at least c IgG molecules bound per antigen is

$$p_G(\rho_G, a) = \sum_{i=2c}^{\tilde{\rho}_0} \binom{\tilde{\rho}_0}{i} \left(\frac{\tilde{\rho}_G}{\tilde{\rho}_0}\right)^i \left(1 - \frac{\tilde{\rho}_G}{\tilde{\rho}_0}\right)^{\tilde{\rho}_0 - i} \tag{13}$$

where $\tilde{\rho}_G \triangleq \rho_G/a$ and $\tilde{\rho}_G \geq 2c$ for c IgG molecules to be bound. Using the De-Moivre Laplace theorem one can show

$$p_G = \frac{1}{2} \operatorname{erf}\left(\frac{\tilde{\rho}_0 - \tilde{\rho}_a}{\sqrt{2\tilde{\rho}_G(1 - \tilde{\rho}_G/\tilde{\rho}_0)}}\right) - \operatorname{erf}\left(\frac{2c - \tilde{\rho}_G}{\sqrt{2\tilde{\rho}_G(1 - \tilde{\rho}_G/\tilde{\rho}_0)}}\right) \tag{14}$$

In deriving (12) and (14) I have relied on the fact that $\tilde{\rho}_0$ is typically 10^5 and hence much greater than $\tilde{\rho}_M$ or $\tilde{\rho}_G$ on live cells.

The optimization problem I wish to consider is minimize the time, i.e.,

$$\min_{u(\cdot), v(\cdot)} \int_0^T dt \tag{15}$$

to go from the initial state:

$$\begin{aligned} &L_M(0) = L_{M0}, \quad L_G(0) = L_{G0}, \; M(0) = G(0) = 0, \quad a(0) = a_0 \\ &\hat{a}(0) = \rho_M(0) = \hat{\rho}_M(0) = \rho_G(0) = \hat{\rho}_G(0) = 0 \end{aligned} \tag{16}$$

to the final manifold:

$$a(T) = a^* \qquad (\text{e.g., } a^* < 1 \text{ antigen/animal}) \tag{17}$$

subject to the dynamic constraints of Eqs. (1) - (10) and the static constraints

$$0 \leq u(t) \leq 1, \quad 0 \leq v(t) \leq 1, \quad t \in [0,T] \tag{18}$$

Results

If a_0 is too large the antigen grows without bound and the final manifold cannot be reached. For smaller values of a_0, using numerical techniques, I have compared the times needed to reach a^* for the following strategies: 1) secrete only IgM 2) secrete IgM and then switch

to IgM secretion. Here I shall only report results for a typical set of biologically reasonable parameter values. A more complete discussion of results, including a study of parameter sensitivity, will be published elsewhere.

As a typical parameter set I have chosen $b = d = 0.1\ h^{-1}$, $s = 3.6 \times 10^6$ antibodies h^{-1}, $\gamma = 5$, $\mu_M = 0.03\ h^{-1}$, $\mu_G = 0.006\ h^{-1}$, $r = 0.5\ h^{-1}$, $\mu_a = 2.0\ h^{-1}$, $\beta_a = 0.693\ h^{-1}$, $k_M = 3.6 \times 10^{-11}$ cm^3 molecule^{-1} h^{-1}, $k_M' = 4.32 \times 10^5\ h^{-1}$, $k_G = 3.6 \times 10^{-11}$ cm^3 molecule^{-1} h^{-1}, $k_G' = 1.44\ h^{-1}$, $c = 32$ and $\tilde{\rho}_0 = 4 \times 10^3$. Concentrations are expressed in molecules or cells per cm^3. I have assumed the immune response is occurring in a mouse with a serum volume of 1.25 cm^3. Further, c and ρ_0 have been chosen to represent a pathogen, such as a bacteria, with a surface area 1/25 that of a red blood cell. Using these parameters I show in Figure 3 how the final time T varies with the time t_s at which the control switches from u = 1, v = 0 to u = 0, v = 1 (IgM to IgG switch) for varying initial concentrations of a_0, with $L_{M0} = 1 \times 10^6$ cells/cm^3 and $L_{G0} = 0$. For $a_0 > 2 \times 10^{11}$ cells/cm^3 the antigen grows without bound.

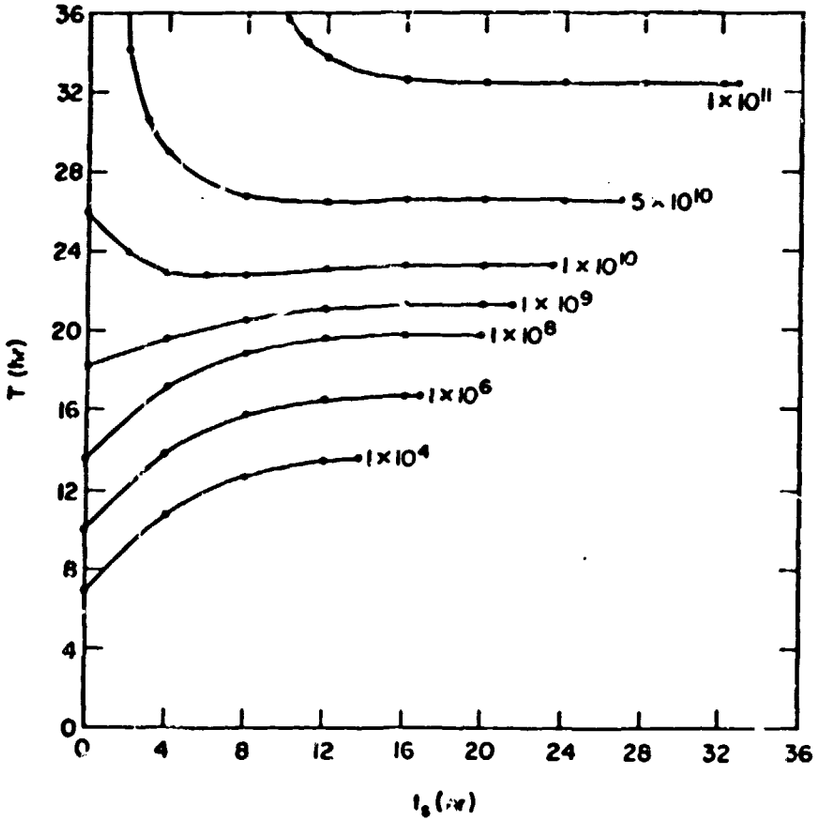

Figure 3. The final time vs the switching time for an immune response employing an IgM-IgG switch. The case of no switch, i.e., IgM production only, corresponds to the last point on each curve where $t_s = T$. Initially, $L_{M0} = 1 \times 10^6$ cells/cm^3, $L_{G0} = 0$, and a_0 was varied between 1×10^{11} cells/cm^3 to 1×10^4 cells/cm^3. The value of a_0 is indicated next to each curve in the figure.

With somewhat smaller values of a_0 the antigen can be destroyed only if the switch to IgG production is delayed beyond some critical time (e.g., approximately 1.6 h for $a_0 = 5 \times 10^{10}$ cells/cm^3). Thus early IgM production is crucial. For each antigen concentration there is some optimal time to switch to IgG production; which minimizes the total response time T. When $a_0 \leq 1 \times 10^9$ cells/cm^3 the optimal switching time is zero, whereas for $a_0 = 1 \times 10^{10}$, 5×10^{10}, and 1×10^{11} cells/cm^3 the optimal switching times are roughly 6 h, 12 h, and 20 h, respectively.

In Figure 4 I illustrate the effects of beginning an immune response with cells that secrete IgG and then switching at time t_s to the production of L_M cells. If $a_0 \geq 5 \times 10^{10}$ cells/cm^3 (not shown) then for a pure IgG response or for any choice of switching time the antigen grows without bound. For $a_0 = 6 \times 10^9$ cells/cm^3 the antigen can be controlled only if a switch to IgM production is made very early. When $a_0 \leq 1 \times 10^9$ cells/cm^3 IgG is sufficiently effective that switching to IgM production has no effect on the total response time. Another type

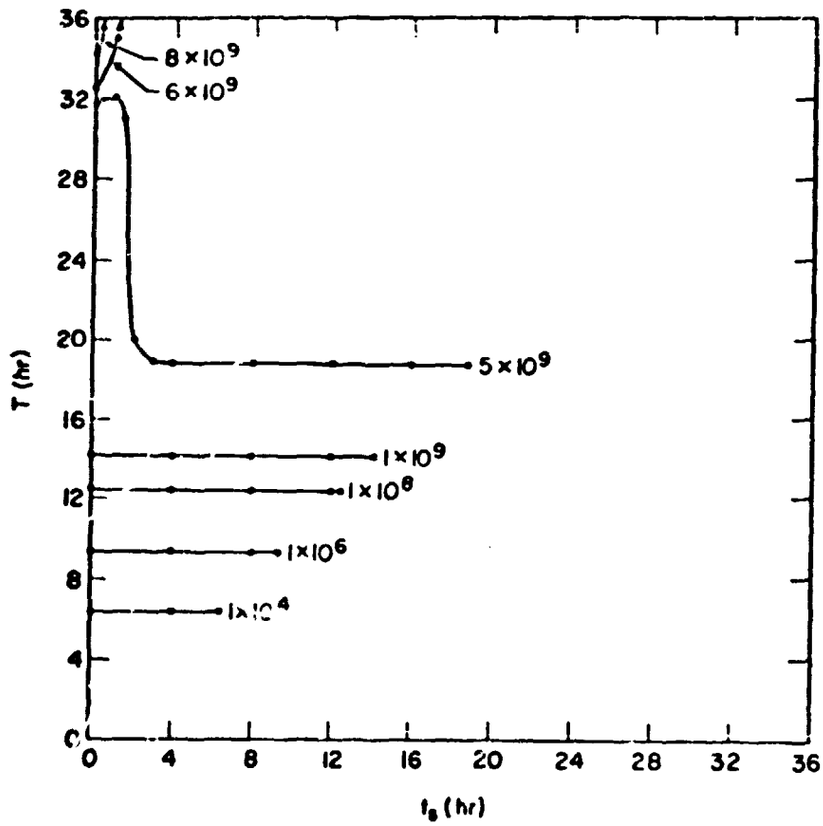

Figure 4. The final time vs the switching time for an immune response employing an IgG-IgM switch [i.e., $u(t) = 0$, $v(t) = 1$, $0 \leq t < t_s$; $u(t) = 1$, $v(t) = 0$, $t_s < t \leq T$] with $L_{M0} = 0$. $L_{G0} = 1 \times 10^4$ cells/cm^3

of behavior occurs when $a_0 = 5 \times 10^9$ cells/cm^3. Here a switch to IgM production at t = 0 considerably lengthens the response; the L_G population is being depleted, so killing by IgG is initially ineffective and there is a long delay ($\sim$ 12 h) before the L_M population is sufficiently large to prevent the antigen population from increasing. However, if the switch is delayed or if only IgG is secreted, then enough IgG is produced to quickly control the antigen.

Comparing Figures 3 and 4 one notices that for $a_0 < 1 \times 10^9$ cells/cm^3 the total response time T is less for pure IgG immune responses than for responses which employ an IgM-IgG switch. Thus for "low" antigen doses it is better to employ a pure IgG response while for "high" antigen doses an IgM-IgG switch is better. In fact, employing a pure IgG response at "high" doses can be a fatal mistake. Here "high" and "low" doses are defined relative to the initial lymphocyte populations, L_{M0} and L_{G0}, since the ratio of bound antibodies to antigens is the crucial parameter in determining cell lysis. Thus if L_{G0} is large enough one would expect that a pure IgG response would be effective against all realizeable antigen concentrations and consequently would be a good strategy. However, if the initial lymphocyte population is low then it would seem best to employ an IgM-IgG switch since an animal may be confronted with a "high" antigen dose. In fact, this divergence in strategies is observed biologically. When the same antigen is encountered by an animal for a second time (the secondary response) the immune system has ready a large population of lymphocytes able to react with the antigen and the immune response is observed to be almost a total IgG response. In contrast, when an antigen is encountered by an animal for the first time (the primary response) a much smaller number of lymphocytes are able to react with the antigen and a switch in the type of antibody from IgM to IgG is usually observed.

Conclusions

For $a_0 \leq 10^{11}$ cells/cm^3 and the other biologically reasonable parameter values used to generate Figures 3 and 4 one can draw the following conclusions:

1) It is better to begin an immune response with L_M cells rather than L_G cells if the antigen concentration is high ($a_0 > 1 \times 10^9$ cells/cm^3).

2) Beginning with only L_M cells one can always reduce the time needed to eliminate the antigen by switching to IgG production at an appropriate time.

3) At high antigen doses switching from IgM to IgG production too early can allow the antigen to grow unbounded, switching too late or not at all only lengthens the response time.

4) At low antigen doses it is always better to begin the immune response with L_G cells. Switching these L_G cells into L_M cells provides no advantage to the animal.

If complement dependent killing of pathogenic organisms were an important defense strategy over evolutionary time, then it seems reasonable that natural selection would have led to the development of an IgM-IgG switch for the primary immune response, and an all IgG secondary response. Whether more complicated switching strategies or singular control would lead to an even more efficient response is not yet known.

References

Borsos, T. and Rapp, H. J. (1965a). J. Immunol. 95, 559-566.

Borsos, T. and Rapp, H. J. (1965b). Science 150, 505-506.

DeLisi, C. (1975a). J. Theor. Biol. 52, 419-440.

DeLisi, C. (1975b). J. Math. Biol. 2, 317-331.

Goldstein, B. and Perelson, A. S. (1976). Biophysical Chem. 4, 349-362.

Hornick, C. L. and Karush, F. (1972). Immunochem. 9, 325-340.

Humphrey, J. H. (1967). Nature 216, 1295-1296.

Humphrey, J. H. and Dourmashkin, R. R. (1965). In Ciba Found. Symp. Complement (eds. Wolstenholme, G.E.W. and Knight, J.) Churchill, London, pp. 175-189.

Mayer, M. (1973). Sci. Am. 229 (No. 5), 54-66.

Mims, C. A. (1976). The Pathogenesis of Infectious Disease, Academic Press, London.

Osler, A. G. (1976). Complement: Mechanisms and Function, Prentice Hall, Englewood Cliffs, New Jersey.

Oster, G. F. and Wilson, E. O. (1978). Ecology and Evolution of Castes in Social Insects, Princeton University Press, Princeton, NJ.

Perelson, A., Mirmirani, M. and Oster, G. (1976). J. Math. Biol. 3, 325-367.

Porter, D. D. (1971). Ann. Rev. Microbiol. 25, 283-290.